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Supporting Information
Gadolinium Complexes of Macrocyclic Diethylenetriamine-N-oxide Pentaacetic Acid-Bisamide as Highly Stable MRI Contrast Agents with High Relaxivity

Materials and Methods

All the solvents were purchased from commercial resources and used as received except for N,N-dimethylformamide (DMF), which was dried over calcium hydride and distilled before used. Diethylenetriamine-pentaacetic-acid-dianhydride (DTPAA) was prepared according to literature procedures.[1]

NMR spectroscopy

^{1}H (400 MHz) and ^{13}C NMR (400 MHz) spectra were recorded on an Ultra Shield 400 spectrometer (Bruker BioSpin AG, Magnet System 400 MHz/54 mm) in D_2O.

Mass spectrometry

Electrospray ionization mass spectrometry (ESI-MS) was employed on an Xevo G2 TOF/MS spectrometer, Waters, USA. The mass spectra of the Gd(III) complexes were recorded on a MALDI/TOF MS spectrometer (Advanced Business System Ltd, Singapore).

Hydration number measurement

Samples with the same concentration of europium complex but different volumetric ratios of H_2O versus D_2O (2:8, 4:6, 5:5, 6:4, 8:2, 10:0) were prepared. Europium luminescence intensities were measured on a fluorescence spectrometer (Edinburgh Instruments FLS 980) with a 50 μs interval at 616 nm for Eu (excitation at 395 nm). The decays of luminescence intensities followed systematically monoexponential laws and were analyzed as single-exponential decays to calculate the europium luminescence lifetime (τ) which was plotted as $1/\tau$ versus χ (i.e., $\chi=V_{H2O}/V$ where V, V_{H2O} and V_{D2O} are the total volume of H_2O and D_2O, the volume of H_2O and the volume of D_2O, respectively). Then $1/\tau$ of H_2O versus D_2O at 0:10 ($1/\tau_{D2O}$) was extrapolated and the hydration number was calculated using the following equation:

$$q = 1.05\left(\frac{1}{\tau_{H_2O}} - \frac{1}{\tau_{D_2O}}\right) - 0.25$$

T_1 relaxivity

T_1 relaxivity measurements were performed on a 1.5 T GE SIGNA EXCITE (GE Medical Mixtures, USA) at ambient temperature. The samples were diluted to different concentrations in 1.5 mL centrifuge tubes. For T_1 measurements, the samples were imaged collectively with a high-resolution inversion recovery pulse sequence (repeat time (T_R) = 1600 ms, echo time (T_E) = 11 ms, inversion time (T_I) = 50, 100, 200, 300, 400, 600, 700, 900, 1200, 1500 ms respectively. Field of view (FOV) = 150 mm◊150 mm, matrix = 320◊320). The resulting images were analyzed on a pixel-by-pixel basis to a single exponential model. These T_1 values were averaged over at least 45 pixels in the center of each sample and plotted as $1/T_1$ versus $[Gd^{3+}]$. The slope of the plot represents the relaxivity, r_1.

General method for the determination of pM values by competition batch titration for ML complexes

Different volumes of a standardized DTPA stock solution were mixed with solutions of **4d** to reach constant concentrations of ligands, metal, and electrolytes. In this work, the pH of all solutions was kept constant at 7.4 with a HEPES buffer and the solutions were diluted to identical volumes. After stirring the solutions for 3 days to ensure that thermodynamic equilibrium was reached, the pH was again checked just before analyzing the samples with spectrophotometry. The concentrations of each ligand relative to DTPA used in the final data analysis ranged from 1:0.1 to 1:10 (L/DTPA). Concentrations of free and complexed ligands in each solution were determined from the absorption spectra. Spectra of free and fully complexed ligands at identical pH value and concentration were used as references for the analysis. These determined concentration values were used in the log/log plots to give the difference in pGd between the competing DTPA and ligand of interest.

Transmetallation kinetics

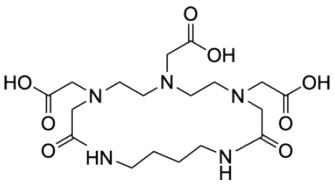
The kinetic inertness of Gd-complexes against transmetallation was evaluated *in vitro* in comparison with Gd-DTPA. Firstly, 10 mL of 2.5 mM Gd complex in phosphate buffer and 100 μL of a 250 mM aqueous solution of $Zn(NO_3)_2 \cdot 6H_2O$ were mixed. The mixture was stirred and samples (0.3 ml) were collected at 2, 4, 6, 8, 10, and 24 h and filtered afterwards. The concentration of Gd(III) in the supernatant was measured by ICP-AES. The kinetic inertness was determined as the percentage of the bound Gd(III) post-incubation to the value before incubation.

Synthesis

General procedure for the synthesis of macrocyclic diethylenetriamine pentaacetic acid-bisamides (**2a**–**2d**)

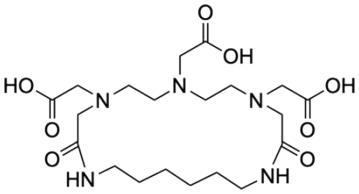
DTPAA (2.28 mmol) was added to a 200 mL Schlenk flask. After charged with DMF (100.0 mL), the flask was sealed under N_2 atmosphere. Then amine (2.5 mmol) dissolved in DMF (20.0 mL) was added to the solution dropwise, followed by stirring for 24 h at 25 ºC. Then the solution was acquired through filtration. After evaporation of the solvent under vacuum, the yellow oil was dissolved in a small amount of DMF, and reprecipitated from THF to afford white solid.

Compound 2a



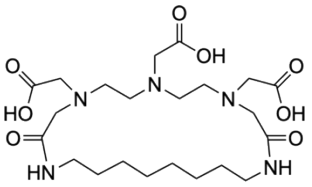
The reaction was performed between DTPAA and 1,4-butanediamine. ^{1}H NMR (D_2O+NaOD, ppm): 2.95-2.88 (m, 12H), 2.82-2.80 (m, 2H), 2.33-2.27 (m, 8H), 1.25 (s, 4H). ^{13}C NMR (D_2O+NaOD, ppm): 179.4, 174.3, 171.1, 67.8, 59.1, 51.5, 38.5, 36.6, 26.4. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 444.2094; found: 444.2093.

Compound 2b



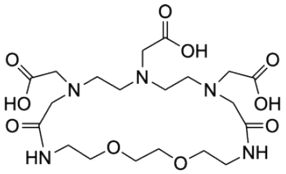
The reaction was performed between DTPAA and 1,6-diaminohexane. ^{1}H NMR (D_2O+Na_2CO_3, ppm): 3.03-2.97 (m, 12H), 2.90-2.88 (m, 2H), 2.47-2.37 (m, 8H), 1.32 (t, 4H), 1.11 (t, 4H). ^{13}C NMR (D_2O+Na_2CO_3, ppm): 179.2, 174.1, 164.8, 67.7, 59.4, 52.9, 38.3, 36.9, 31.4, 28.1, 25.4. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 472.2407; found: 472.2486.

Compound 2c



The reaction was performed between DTPAA and 1,8-diaminooctane. ^{1}H NMR (D_2O+Na_2CO_3, ppm): 3.23-3.01 (m, 14H), 2.66-2.50 (m, 8H), 1.44 (s, 4H), 1.32-1.20 (m, 8H). ^{13}C NMR (D_2O+Na_2CO_3, ppm): 179.4, 179.1, 178.6, 174.3, 173.7, 164.9, 67.8, 59.5, 59.0, 58.6, 57.9, 52.8, 52.7, 52.3, 39.0, 38.7, 36.9, 31.4, 27.9, 26.2, 25.5. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 500.2720; found: 500.2717.

Compound 2d

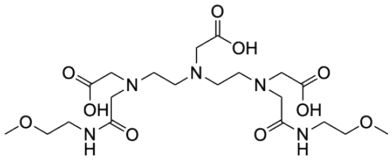


The reaction was performed between DTPAA and 2,2'-(ethylenedioxy)diethylamine. ^{1}H NMR (D_2O+Na_2CO_3, ppm): 3.63-3.49 (m, 8H), 3.30 (t, 4H), 3.13-2.99 (m, 10H), 2.59-2.49 (m, 8H). ^{13}C NMR (D_2O+Na_2CO_3, ppm): 179.3, 179.1, 178.8, 174.5, 69.5, 69.0, 68.8, 67.8, 59.2, 59.0, 58.5, 58.2, 58.1, 52.4, 38.7, 38.6, 25.0. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 504.2306; found: 504.2305.

Procedure for the synthesis of acyclic diethylenetriamine pentaacetic acid-bisamides (5)[2]

DTPAA (1.0 mmol) was added to a 50 mL Schlenk flask. After charged with dry DMF (5.0 mL), the flask was sealed and heated at 50 ºC under N_2 atmosphere. Then amine (2.2 mmol) was added to the solution dropwise, followed by stirring for 24 h. After evaporation of the solvent under vacuum, the yellow oil was dissolved in water before adjusting the pH to 12.00 to break the hydrogen-bonding interactions between the carboxyl groups and the free amine, thus the excessive amine could be excluded after the evaporation under vacuum. With the aim of changing the sodium carboxylates back into carboxyl groups, the provided solid was dissolved in water again to adjust the pH to 7.0. When the water was evaporated under vacuum, ethanol was added to the mixture and the precipitated NaCl was removed by filtration. Finally, the solution was concentrated *in vacuo* and recrystallized from ethanol/diethyl ether (1:4) to afford a yellow fluffy solid.

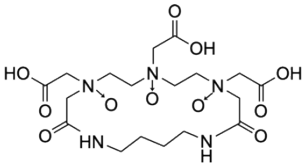
Compound 5



The reaction was performed between DTPAA and 2-methoxyethylamine. ^{1}H NMR (D_2O+NaOD, ppm): 3.57 (t, 4H), 3.43 (t, 4H), 3.36 (s, 6H), 3.33-3.29 (m, 6H), 3.16 (s, 4H), 2.82-2.79 (m, 8H). ^{13}C NMR (D_2O+NaOD, ppm): 179.1, 174.5, 164.9, 79.3, 58.6, 58.5, 58.1, 52.1, 38.5, 36.9, 31.4. Mass spectrum (ESI): M/Z calc. for $[M+Na]^+$: 530.2438; found: 530.2448.

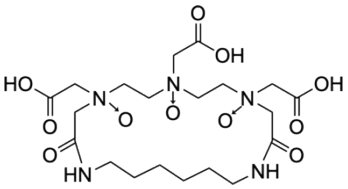
General procedure for the synthesis of macrocyclic diethylenetriamine-N-oxide pentaacetic acid-bisamides (3a-3d) and acyclic diethylenetriamine-N-oxide pentaacetic acid-bisamides (6). Compound **2** (1.5 mmol) was dissolved in acetic acid or methanol (3.0 mL) at room temperature before excessive hydrogen peroxide was added into the solution. After stirring for 72 h, Pd/C catalyst was used to consume the unreacted hydrogen peroxide. Then the mixture was filtered to remove Pd/C catalyst and the filtrate was evaporated to provide yellow oil.

Compound 3a



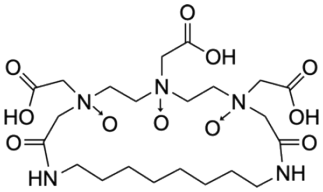
The reaction was performed between **2a** and hydrogen peroxide in acetic acid. ^{1}H NMR (D_2O+Na_2CO_3, ppm): 3.96-2.38 (m, 22H), 1.65 (s, 2H), 1.28 (s, 2H). ^{13}C NMR (D_2O+Na_2CO_3, ppm): 181.5, 171.2, 169.8, 169.6, 164.9, 70.3, 67.3, 38.9, 36.9, 26.0, 25.9, 25.6, 23.4. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 492.1942; found: 492.1943.

Compound 3b



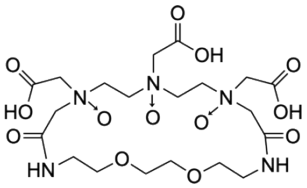
The reaction was performed between **2b** and hydrogen peroxide in acetic acid. ^{1}H NMR (D_2O+Na_2CO_3, ppm): 4.66-3.82 (m, 14H), 1.48 (t, 4H), 1.31 (t, 4H). ^{13}C NMR (D_2O+Na_2CO_3, ppm): 171.1, 169.8, 164.9, 70.2, 66.9, 58.5, 34.0, 36.9, 34.5, 31.4, 27.9, 25.7. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 520.2255; found: 520.2254.

Compound 3c



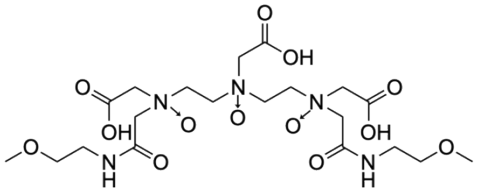
The reaction was performed between **2c** and hydrogen peroxide in acetic acid. ^{1}H NMR (D_2O+Na_2CO_3, ppm): 4.43-3.56 (m, 14H), 3.25-2.59 (m, 8H), 1.43 (t, 4H) 1.25-1.20 (m, 8H). ^{13}C NMR (D_2O+Na_2CO_3, ppm): 170.0, 169.6, 168.9, 164.9, 158.1, 69.7, 60.1, 59.7, 39.4, 36.9, 34.5, 31.4, 28.1, 27.5, 25.9, 25.2. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 548.2568; found: 548.2567.

Compound 3d



The reaction was performed between **2d** and hydrogen peroxide in acetic acid. ^{1}H NMR (D_2O+Na_2CO_3, ppm): 4.62-3.65 (m, 22H), 3.42-2.65 (m, 8H). ^{13}C NMR (D_2O+Na_2CO_3, ppm): 174.0, 173.2, 171.1, 168.4, 72.2, 69.4, 68.8, 68.6, 58.8, 51.9, 51.4, 50.9, 50.4, 39.8, 38.9, 38.7. Mass spectrum (ESI): M/Z calc. for $[M-H]^-$: 552.2153; found: 552.2155. Anal. Calc. for $C_{20}H_{35}N_5O_{13}\cdot 12H_2O$: C, 31.21; H, 7.73; N, 9.10. Found: C, 31.30; H, 7.82; N, 9.23.

Compound 6



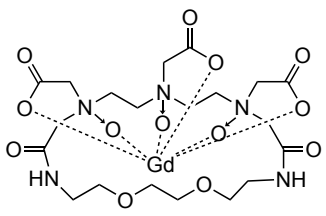
The reaction was performed between **5** and hydrogen peroxide in methanol. ^{1}H NMR (D_2O+NaOD, ppm): 4.42-3.82 (m, 13H), 3.56 (t, 4H), 3.43 (t, 4H), 3.34 (s, 6H). ^{13}C NMR (D_2O+NaOD, ppm): 171.1, 170.0, 169.9, 169.5, 165.6, 73.7, 70.0, 68.7, 68.3, 60.5, 60.1, 59.9, 59.8, 59.6, 58.0, 57.9. Mass spectrum (ESI): M/Z calc. for $[M+Na]^+$: 578.2286; found: 578.2281. Anal. Calc. for $C_{20}H_{37}N_5O_{13}\cdot 9H_2O$: C, 33.47; H, 7.72; N, 9.76. Found: C, 33.64; H, 7.58; N, 9.67.

General procedure for the synthesis of macrocyclic diethylenetriamine-N-oxide pentaacetic acid-bisamide-based Gd(III) complexes (4a-4d).

Macrocyclic diethylenetriamine-N-oxide pentaacetic acid-bisamide (1.00 mmol) in deionized water (20.0 mL) was reacted with $Gd_2(CO_3)_3$ (1.05 mmol) at 100 ºC for 3 days. After removing the excess $Gd_2(CO_3)_3$ by filtration, the solution was dried and the product was obtained as a white powder.

Of all the complexes, only **4d** was obtained in good yield. Others were mixed with inseparable coordination polymers.

Complex 4d

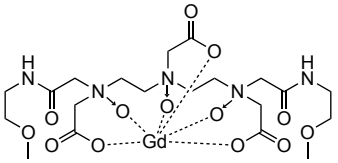


MALDI-TOF: M/Z observed: 708.1215, calculated for: 708.1238 $[M]^+$. Anal. Calc. for $C_{20}H_{32}N_5O_{13}Gd \cdot 14H_2O$: C, 25.02; H, 6.30; N, 7.30. Found: C, 24.87; H, 6.21; N, 7.37.

Procedure for the synthesis of acyclic diethylenetriamine-N-oxide pentaacetic acid-bisamide-based Gd(III) complexes (7).

A solution of $GdCl_3 \cdot 6H_2O$ (1.05 mmol) in methanol (2.0 mL) was added to a stirred solution of acyclic diethylenetriamine-N-oxide pentaacetic acid-bisamide (1.00 mmol) in methanol (10.0 mL). An excess of pyridine (0.8 mL) was added and the suspension was heated at 55 ºC for approximately 24 h. After evaporating the solvent, the mixture was dissolved in water and the pH was adjusted to 10 by adding 0.5 M NaOH in order to precipitate the excessive $Gd(OH)_3$. The mixture was filtered through a 220 nm Millipore filter and recrystallized from ethanol/diethyl ether (1:5) to afford the final product.

Complex 7



MALDI-TOF: M/Z observed: 710.1323, calculated: 710.1394 $[M]^+$. Anal. Calc. for $C_{20}H_{34}N_5O_{13}Gd \cdot 5H_2O$: C, 30.03; H, 5.55; N, 8.76. Found: C, 29.93; H, 5.32; N, 8.58.

Procedure for the synthesis of macrocyclic diethylenetriamine-N-oxide pentaacetic acid-bisamide-based Eu(III) complexes (Eu-3d).

The synthesis of Eu-**3d** follows the same procedure as for **4d**, using $Eu_2(CO_3)_3$ instead of $Gd_2(CO_3)_3$. MALDI-TOF: M/Z observed: 734.1658, calculated: 734.1393 $[M+MeOH-H]^-$.

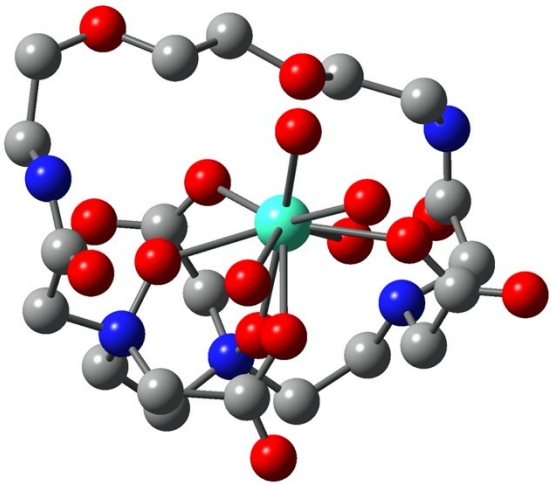


Figure S1. Computational simulated structure of **4d** complex with Gaussian 09.[3]

Table S1. Cartesian coordinates of Gd chelate optimized with B3LYP functional. Stuttgart pseudopotential with quasi-relativistic effect (MWB53) and the correspondent basis set are employed for Gd^{3+} ion, where 53 inner shell electrons are treated with pseudopotential while eight valence electrons are treated explicitly. For other atomic kinds, 6-31G* basis set is employed.

Atomic Symbol	Coordinates (Å)		
	X	Y	Z
Gd	0.085205	0.220838	0.613957
C	-0.439965	-2.682305	-2.515601
H	-0.345249	-2.937758	-3.578189
H	-0.300354	-3.561359	-1.882931
C	-1.847772	-2.069905	-2.320187
H	-1.951546	-1.147109	-2.891093
H	-2.549620	-2.821440	-2.701072
C	2.041763	-2.441769	-2.113370
H	2.273166	-2.781057	-3.130244
H	1.882590	-3.296032	-1.453203
C	3.253302	-1.591581	-1.643035
H	3.529312	-0.821533	-2.363391
H	4.090344	-2.293410	-1.551527
N	3.147956	-0.852656	-0.312171
N	-2.383295	-1.722885	-0.906884
N	0.689529	-1.735823	-2.125518
C	0.728277	-0.462110	-2.983786
H	1.683488	0.015311	-2.786485
H	0.617959	-0.779157	-4.021897
C	-0.371088	0.588620	-2.611929
O	-1.360245	0.716158	-3.372946
O	-0.126064	1.250125	-1.535916

O	0.399515	-1.573228	-0.755806
O	2.199033	0.218385	-0.494037
O	-1.917426	-0.464451	-0.407782
C	4.441733	-0.104981	-0.007599
H	4.428290	0.124796	1.056308
H	5.296569	-0.742283	-0.243147
C	2.849981	-1.805757	0.859075
H	3.700255	-2.486733	0.926101
H	1.915936	-2.322968	0.642165
C	-2.217510	-2.887347	0.079520
H	-2.955980	-2.714241	0.864734
H	-2.438032	-3.802278	-0.473565
C	-3.874570	-1.391932	-1.068779
H	-4.462944	-2.311791	-1.082077
H	-3.970215	-0.837357	-2.000566
C	4.512118	1.151851	-0.881308
C	2.733688	-1.002320	2.187812
C	-0.806900	-2.982317	0.719795
C	-4.245288	-0.534138	0.158569
O	-0.114275	-3.991229	0.486684
O	-4.401322	-1.091468	1.272026
O	3.613080	-1.155433	3.051950
O	4.985962	1.063351	-2.033136
O	-0.514666	-1.985341	1.521941
N	-4.444208	0.788280	-0.024745
H	-4.699060	1.279728	0.825954
N	4.166356	2.353944	-0.327027
H	4.416989	3.133241	-0.930106
O	1.703138	-0.198265	2.245845
C	-4.116741	1.611304	-1.206553
H	-3.136104	1.328484	-1.604400
H	-4.876528	1.451985	-1.981506
C	3.078531	2.635503	0.633006
H	2.825160	1.737257	1.192851
H	3.403318	3.412841	1.329972
C	1.852163	3.101309	-0.192119
H	1.777936	2.499058	-1.098983
H	1.945847	4.166053	-0.439984
C	-4.099557	3.124144	-0.838070
H	-4.645972	3.289036	0.105466
H	-4.591538	3.697704	-1.624899
O	0.582143	2.903380	0.548666
O	-2.774934	3.704789	-0.761207
C	-0.509965	3.657581	-0.136037

H	-0.420678	4.712191	0.139357
H	-0.397710	3.515665	-1.210830
C	-1.892660	3.103749	0.230532
H	-2.209651	3.359708	1.246782
H	-1.912991	2.021101	0.111944
O	-0.739674	1.545425	2.459402
H	-0.682570	1.017431	3.373095
H	-0.272073	2.401817	2.483603
O	-2.388087	-1.414395	3.308029
H	-3.229997	-1.140750	2.889027
H	-1.742892	-1.719194	2.610497
O	-0.533572	0.012193	4.384545
H	-1.322188	-0.598231	4.198761
H	0.321175	-0.423949	4.188999

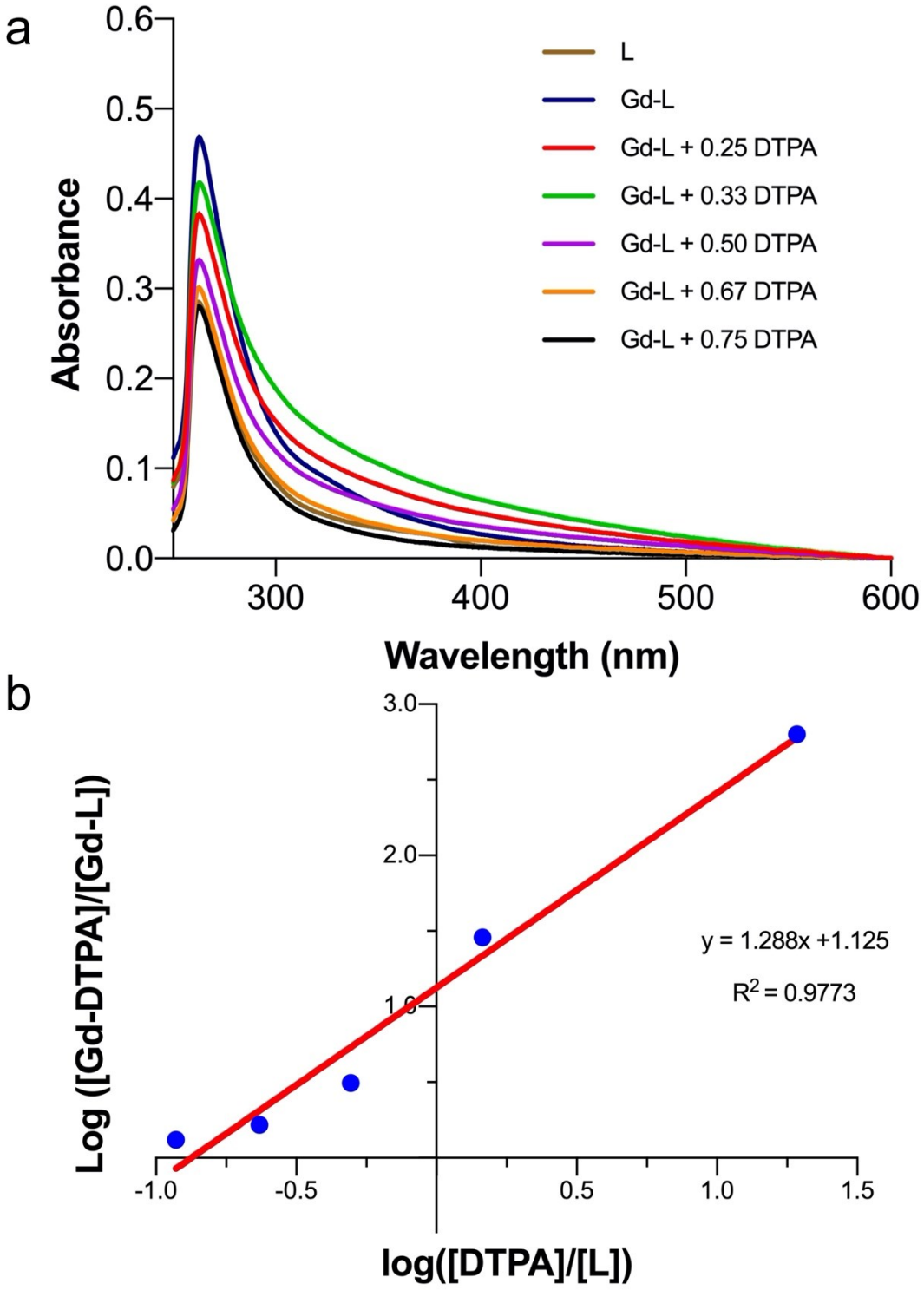


Figure S2. (a) Absorption spectra obtained from competition titration of **6** (L) versus DTPA for Gd(III). Experimental conditions: [L] = [Gd] = 1.5 mM, [DTPA] = 0.375-1.125 mM, pH 7.4, 25 °C, 0.1 M KCl. (b) Competition titration log/log plot for **6** versus DTPA; the x intercept indicates the difference in pGd between **6** and DTPA.

Figure S3. Color photographs of xylenol orange solutions in the presence of 100 μM (a), 50 μM (b), 25 μM (c), 15 μM (d), 10 μM (e), 0 μM (f) of Gd(III) ion and 1 mM **4d** (g), respectively. The concentration of xylenol orange solution is 10 mg/L.

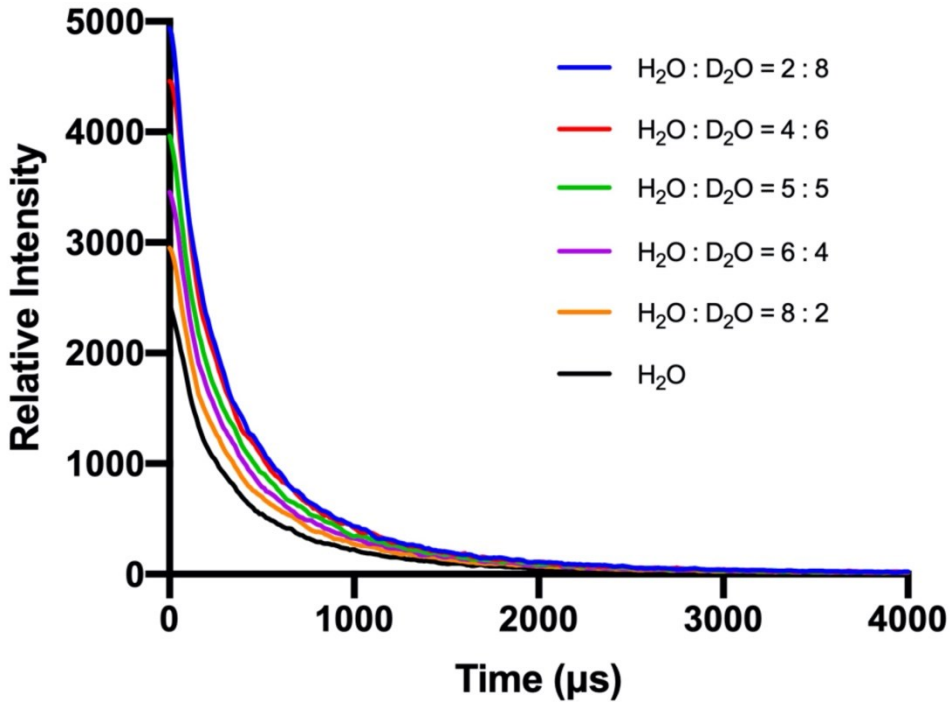


Figure S4. Luminescence decay spectra of Eu-**3d** at different Z_{H2O}.

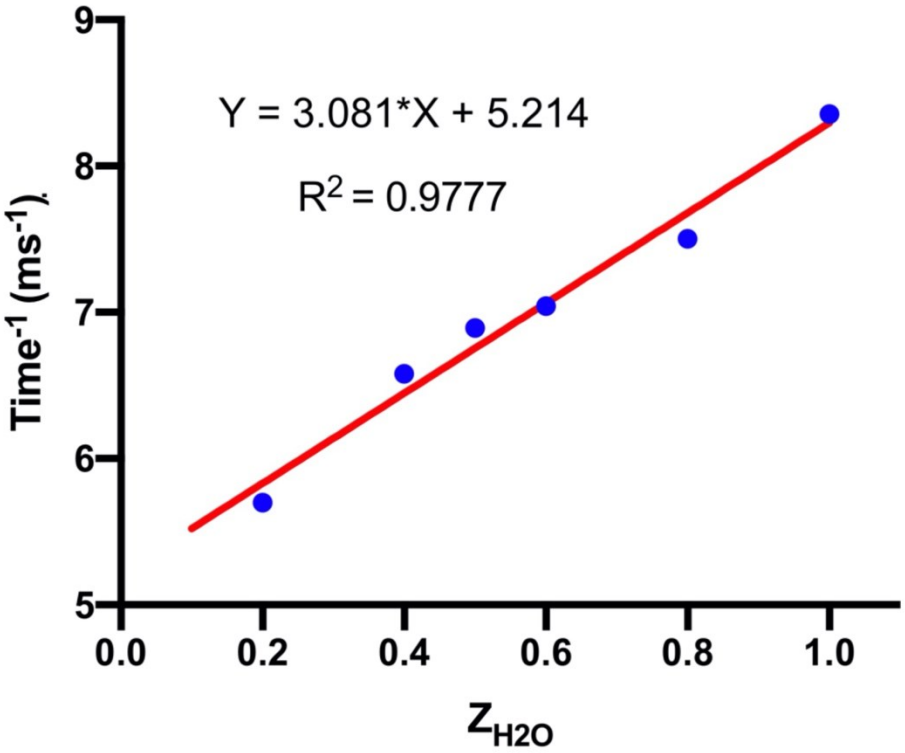


Figure S5. Linear fitting of luminescence lifetimes τ^{-1} of Eu-**3d** and Z_{H2O}.

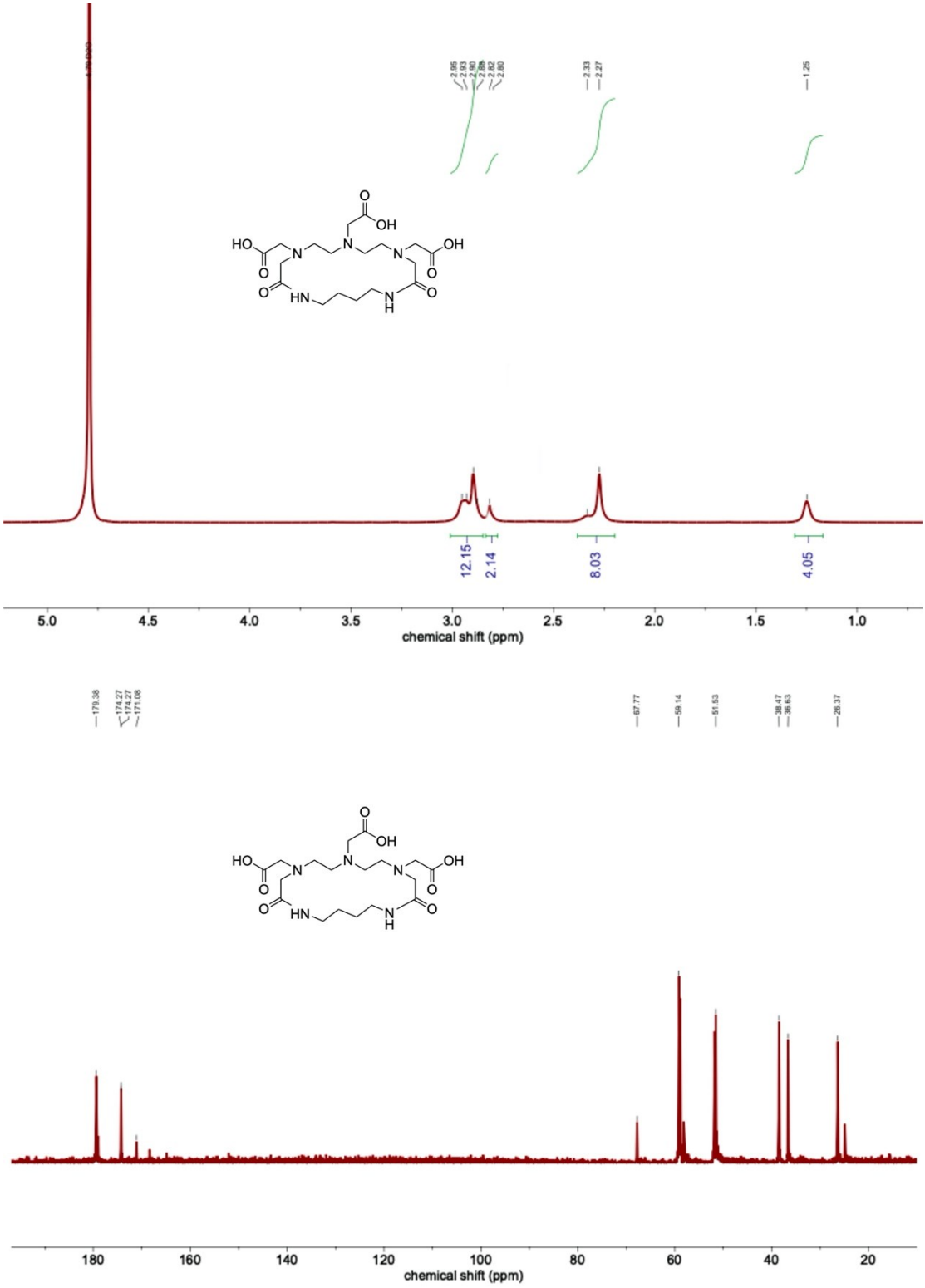


Figure S6. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **2a** in D_2O+NaOD.

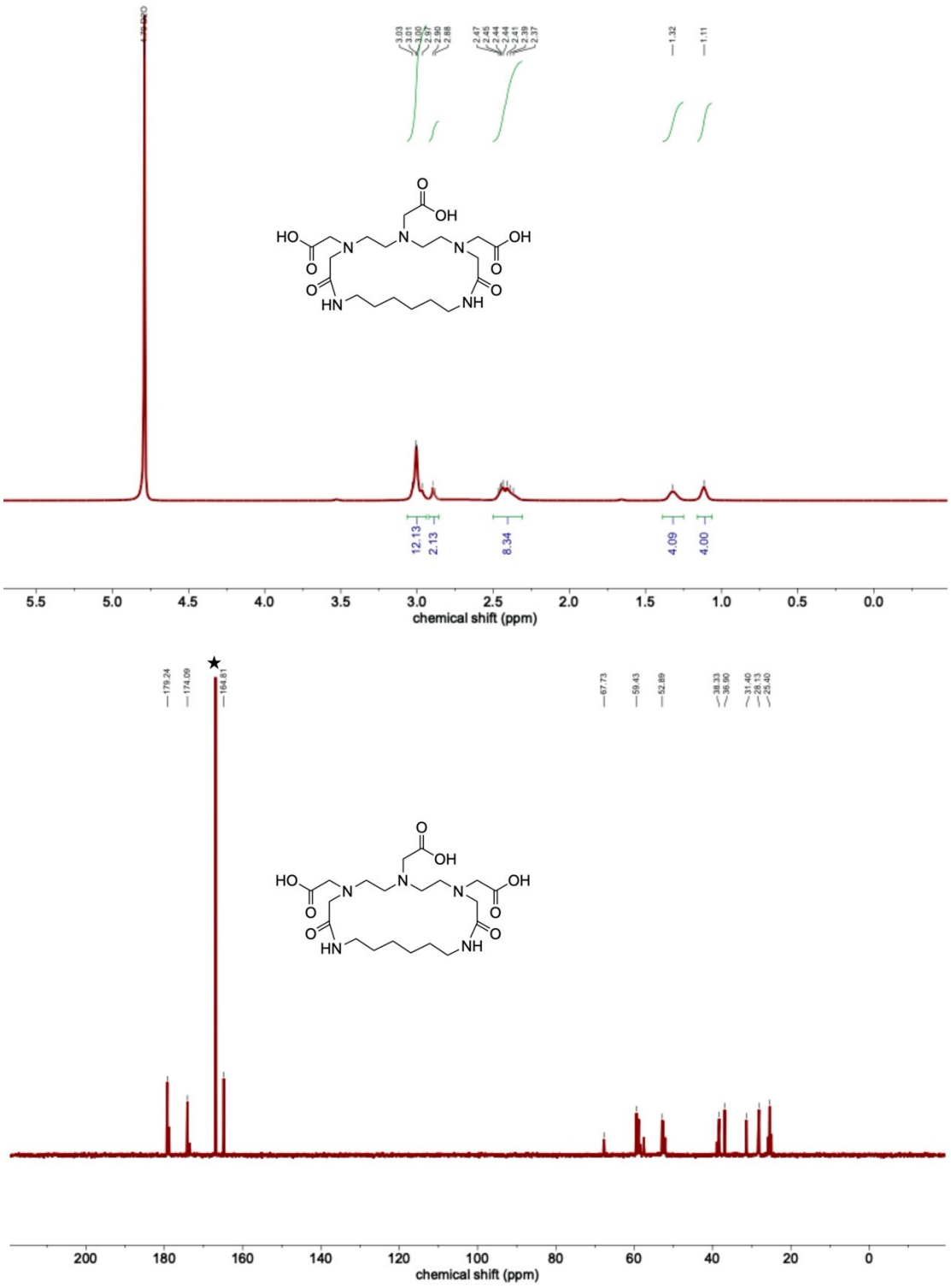


Figure S7. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **2b** in D_2O+Na_2CO_3 (★ indicates Na_2CO_3).

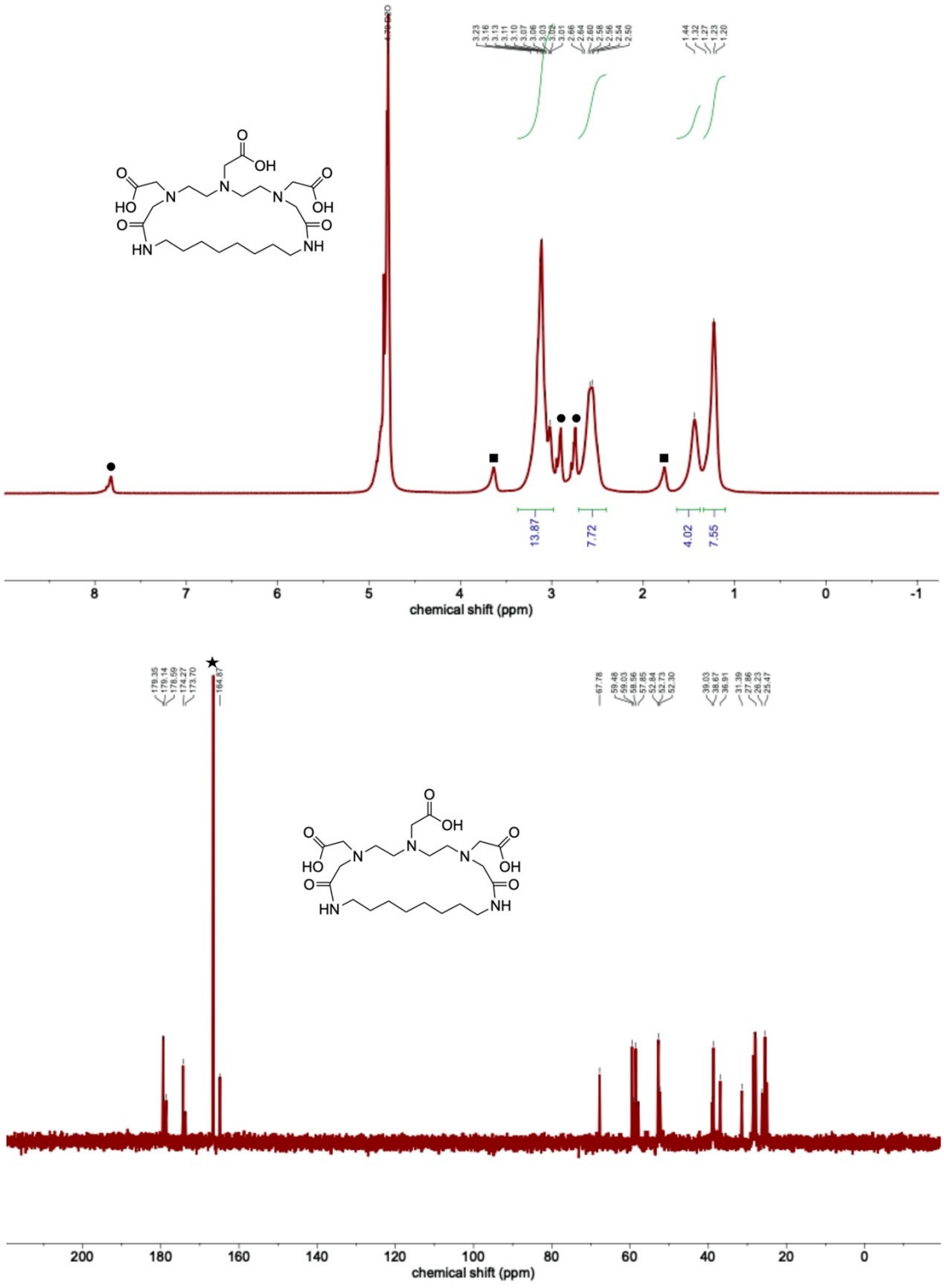


Figure S8. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **2c** in D_2O+Na_2CO_3 (★ indicates Na_2CO_3, ● indicates DMF, ■ indicates ethanol).

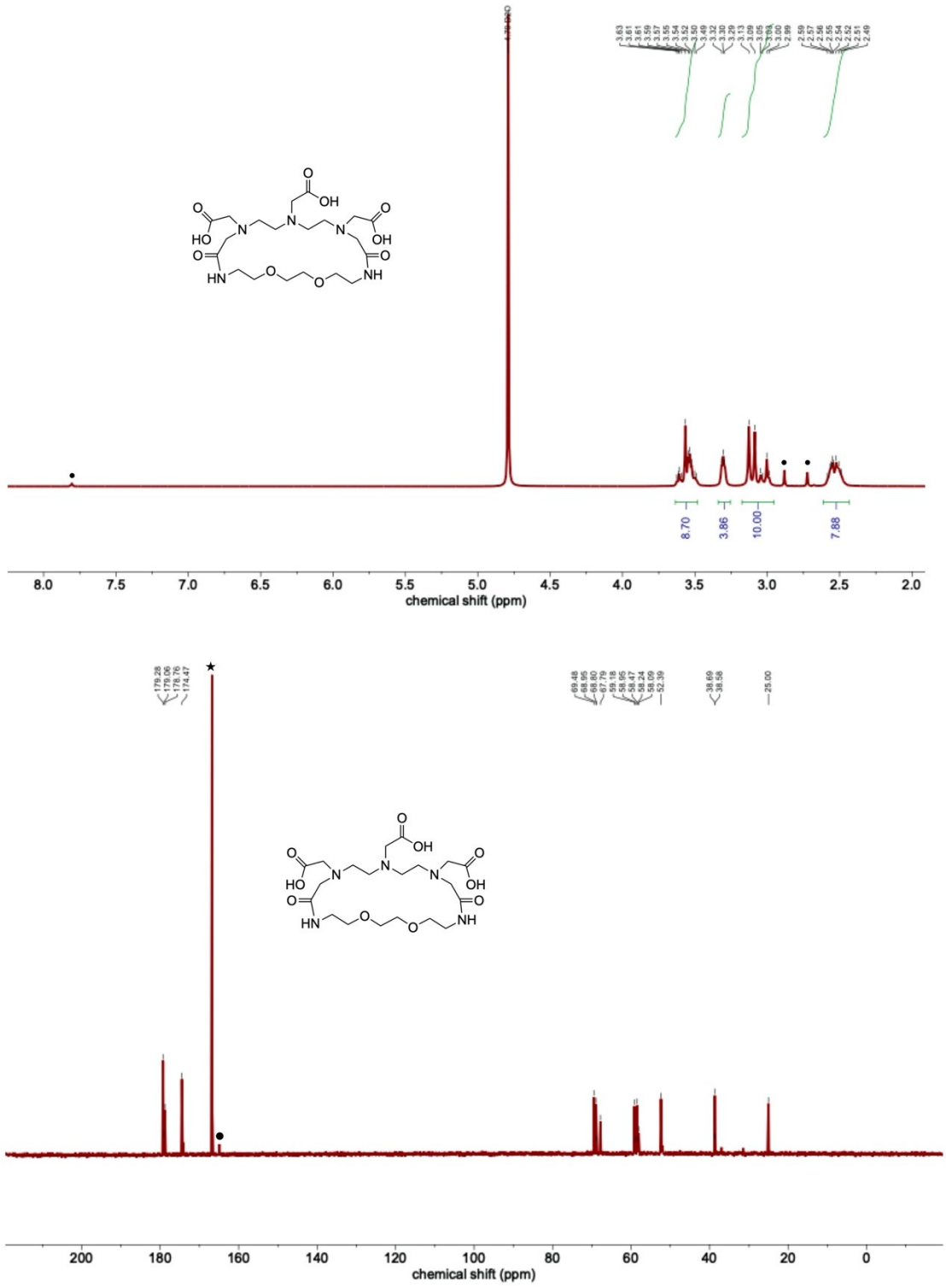


Figure S9. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **2d** in D_2O+Na_2CO_3 (★ indicates Na_2CO_3, ● indicates DMF).

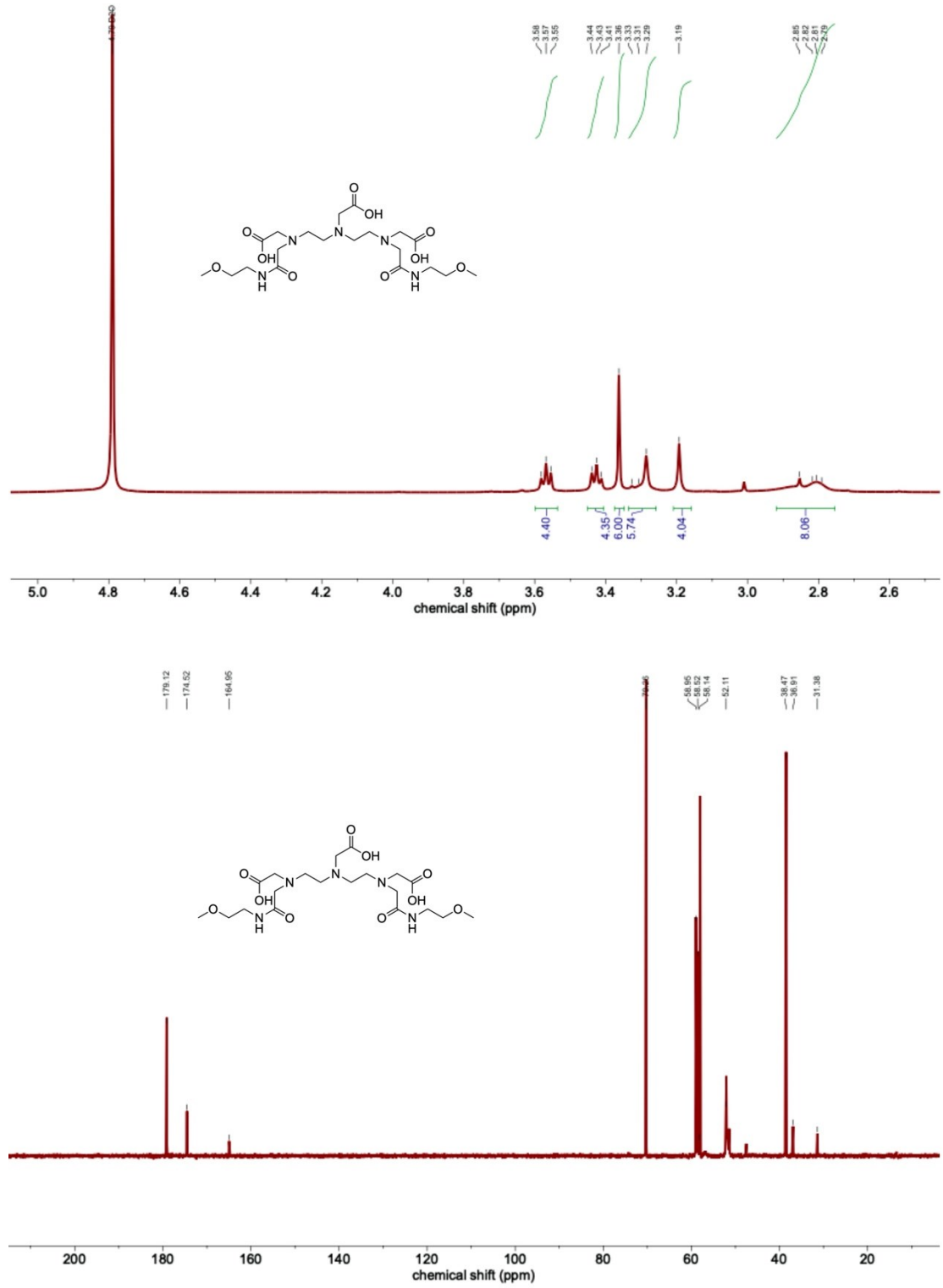


Figure S10. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **5** in D_2O+NaOD

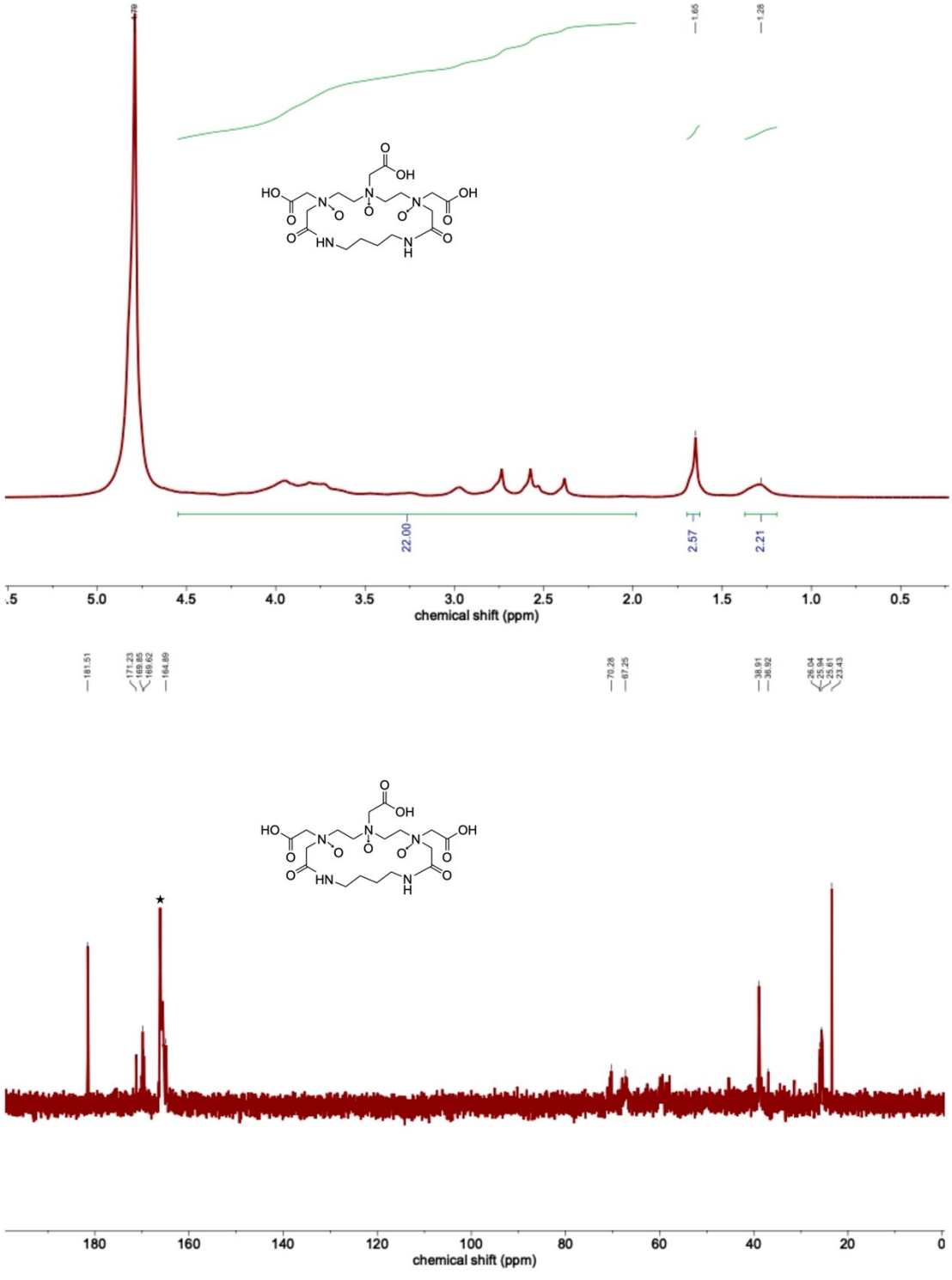


Figure S11. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **3a** in D_2O+Na_2CO_3 (★ indicates Na_2CO_3).

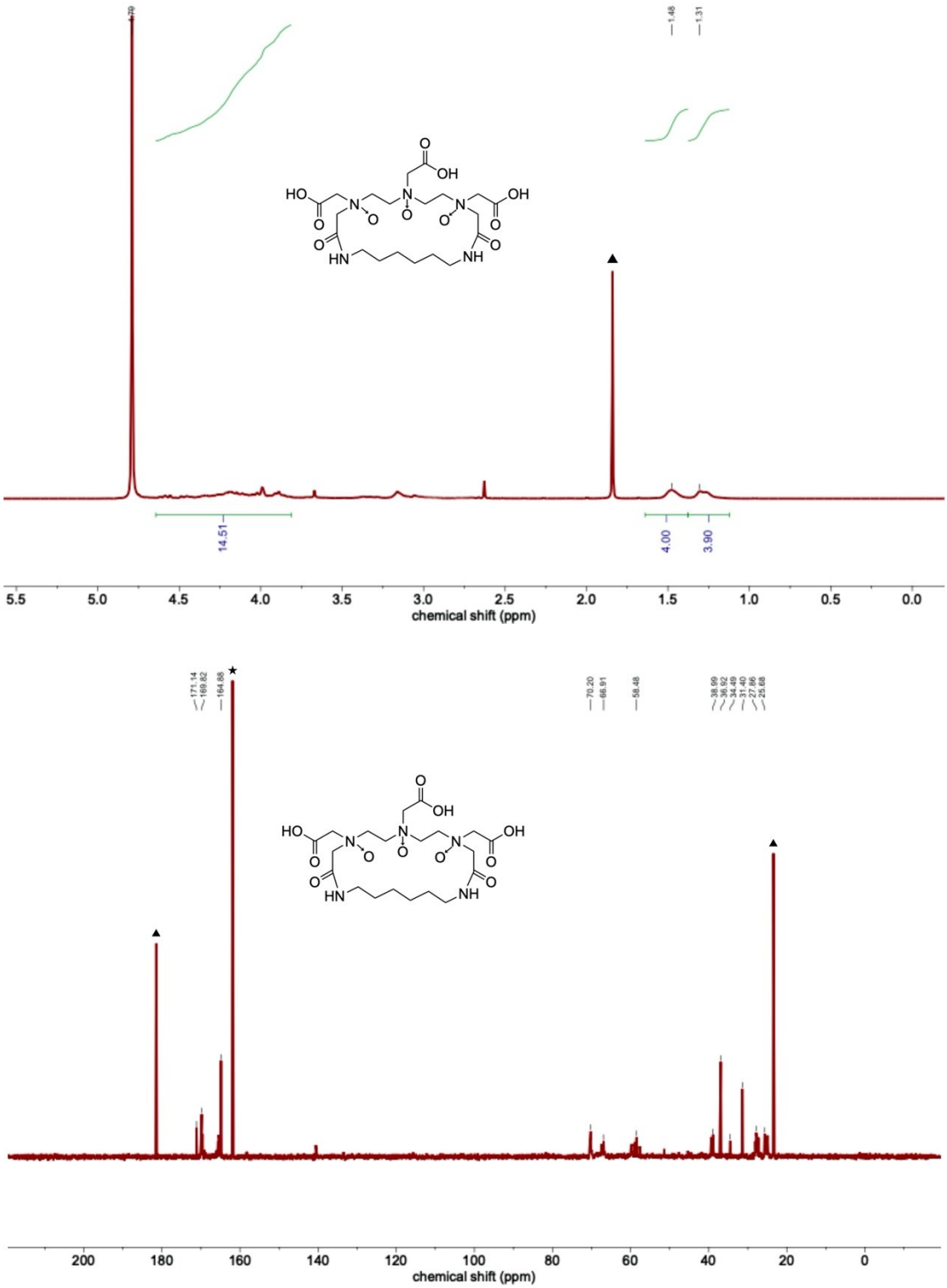


Figure S12. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **3b** in D_2O+Na_2CO_3 (★ indicates Na_2CO_3, ◘ indicates acetic acid).

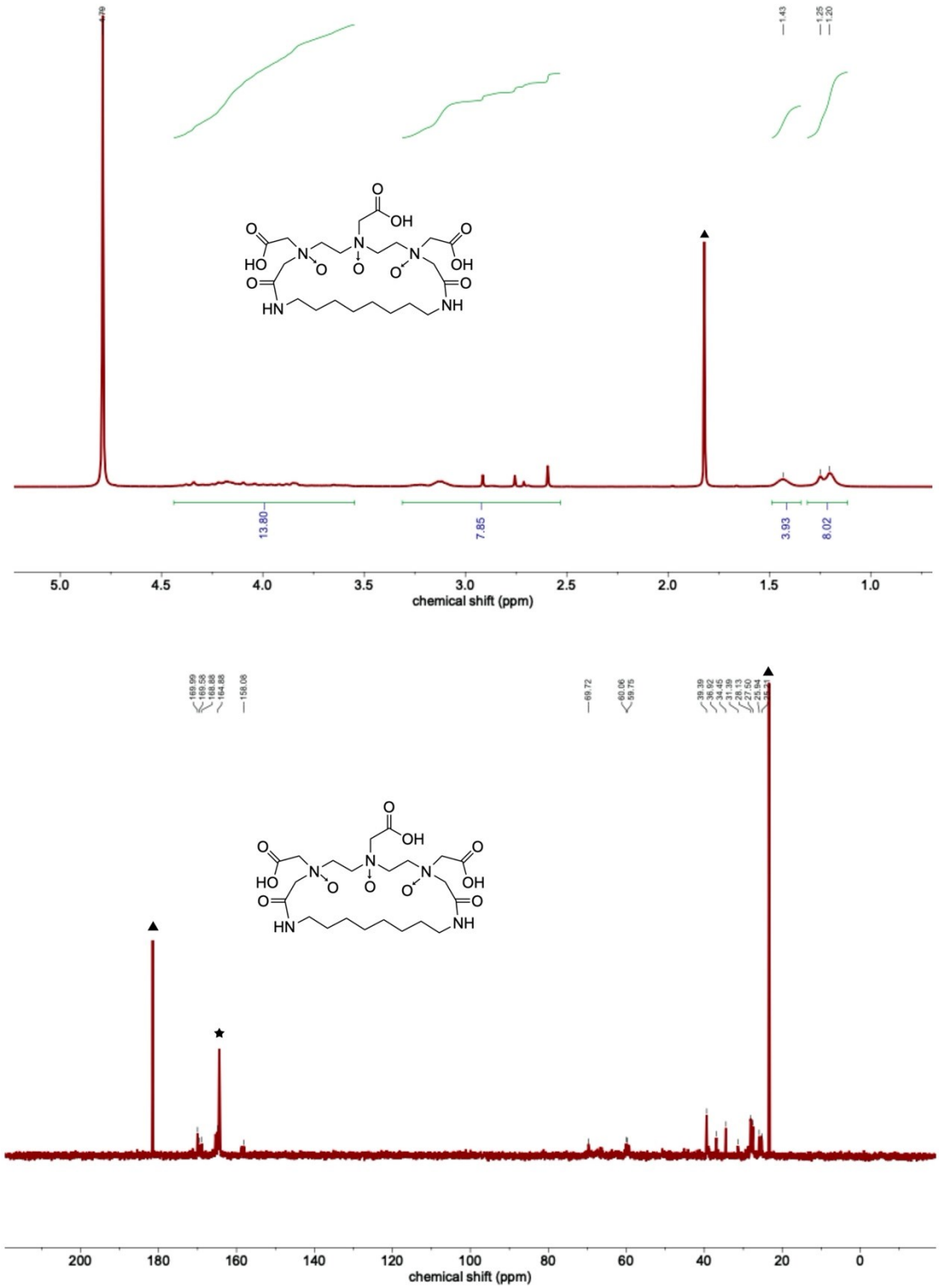


Figure S13. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **3c** in D_2O+Na_2CO_3 (★ indicates Na_2CO_3, ◘ indicates acetic acid).

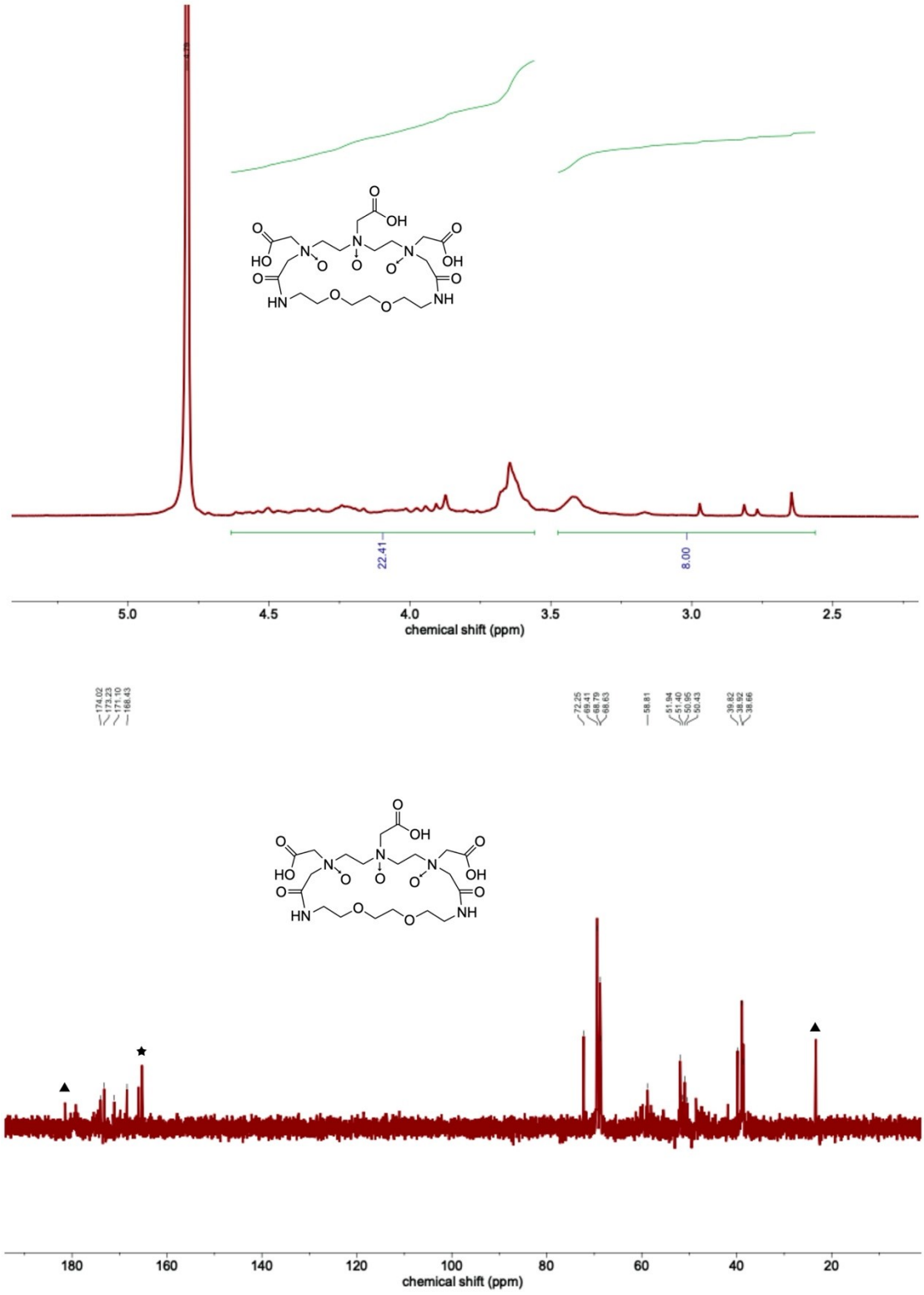


Figure S14. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **3d** in D_2O+Na_2CO_3 (★ indicates Na_2CO_3, ◘ indicates acetic acid).

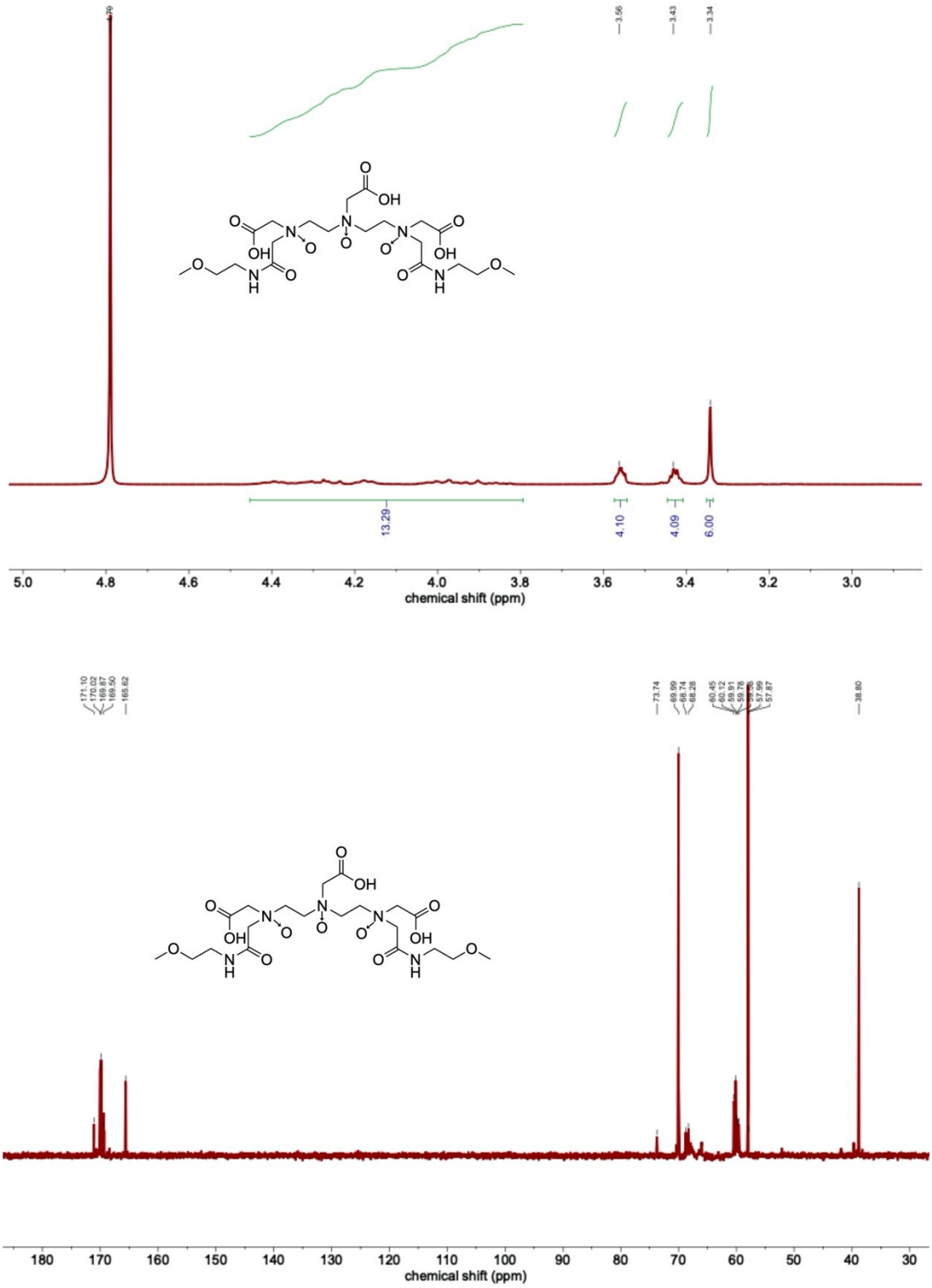


Figure S15. ^{1}H NMR (top) and ^{13}C NMR (bottom) spectra of **6** in D_2O+NaOD.

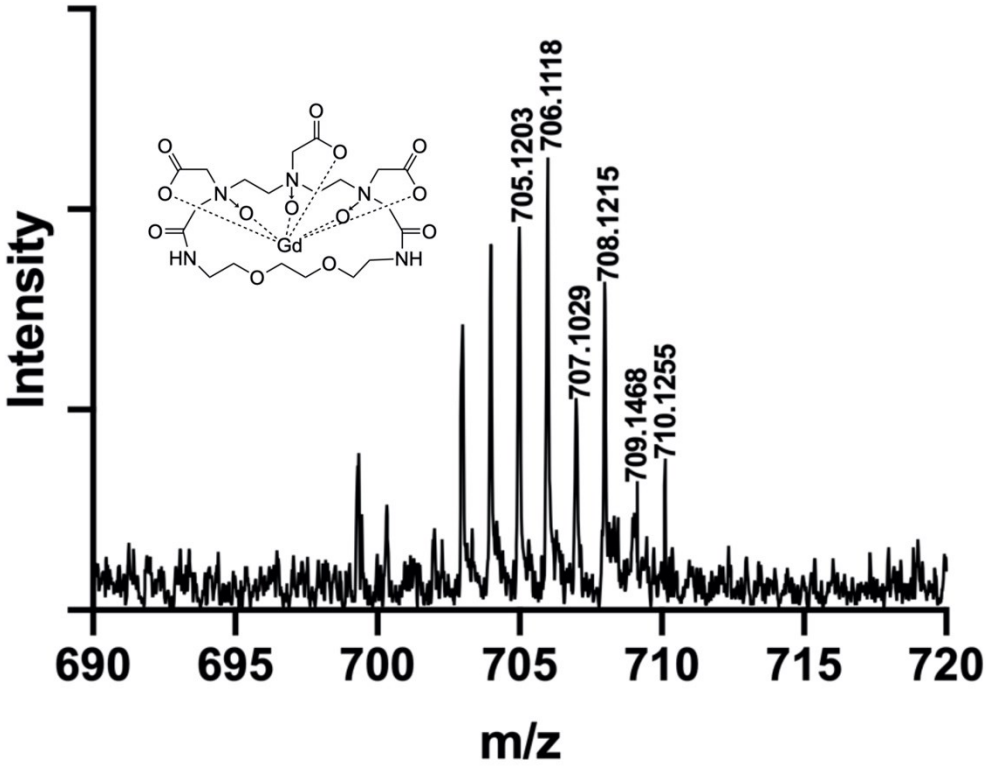


Figure S16. MALDI-TOF mass spectrum of **4d**.

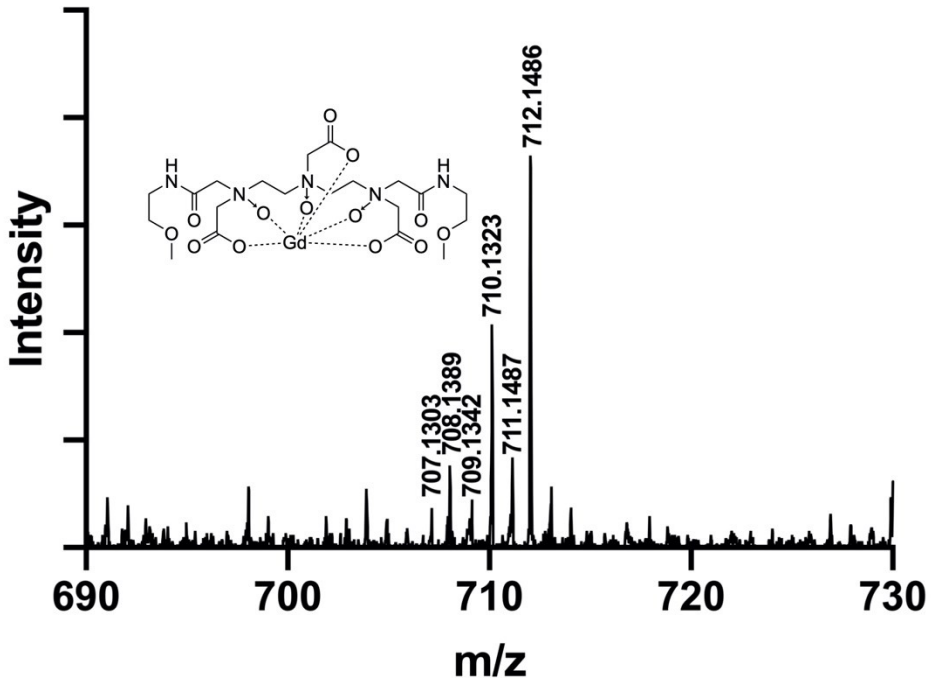


Figure S17. MALDI-TOF mass spectrum of **7**.

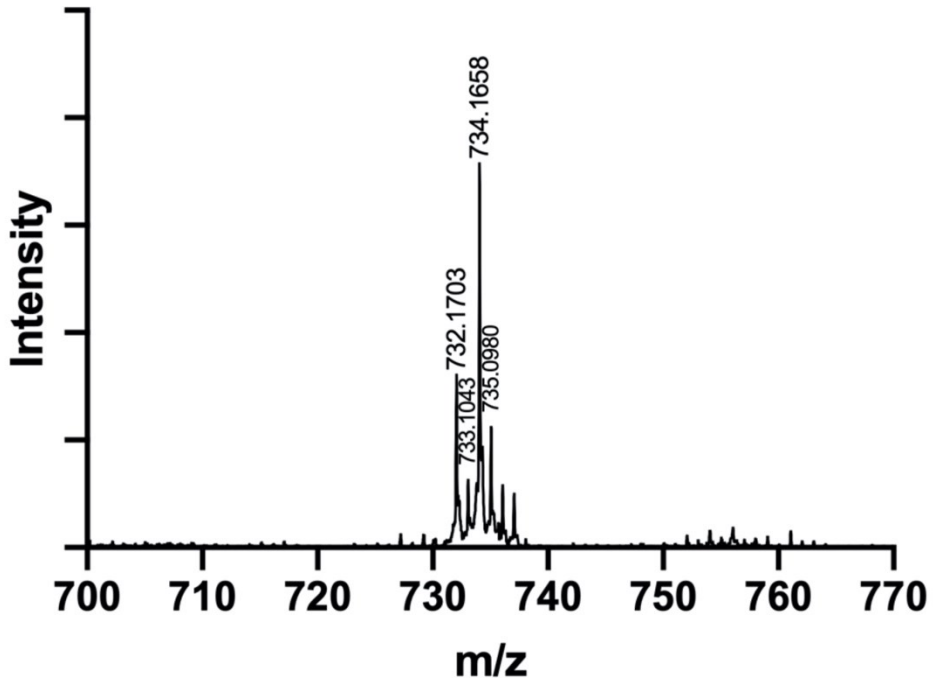


Figure S18. MALDI-TOF mass spectrum of Eu-**3d**.

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